REMARKS

Reconsideration and withdrawal of the claim rejections are requested in view of the amendments and remarks herein.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 4, 5, 16-19 and 21-38 are under consideration in this application. Claims 1, 4, 5, 18 and 19 have been amended; claims 21-38 have been added to round out the scope of protection to which Applicants are entitled. For the Examiner's convenience, a clean copy of the pending claims is appended hereto.

Support for the new and amended claims is found throughout the specification and from the claims. Specifically, support for claims 21-28, 36 and 37 can be found in claim 1, as originally filed, and support for claims 29-35 can be found in claim 5, as originally filed. The remaining amendments were made to place the claims in better form, and are not substantive.

No new matter is added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

Substitute Specification

The substitute specification that was filed on August 8, 2001 was filed in response to the Notice to File Missing Parts, dated June 8, 2001. A substitute specification was required because the original specification contained improper margins. Therefore, the only change between the specification filed on January 19, 2001 and the substitute specification filed on August 8, 2001 was the width of the margins. The substitute specification includes no new matter. Further, it is believed that no marked-up version is required to show modification to the margins. Entry of the substitute specification is requested.

II. THE DOUBLE-PATENTING REJECTION IS ADDRESSED

Claims 1, 4, 5 and 16-19 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 210 and 211 of U.S.S.N. 09/760,574. The rejection is traversed.

Claims 210 and 211 of U.S.S.N. 09/760,574 are directed to method for inducing an immunological response against a bovine pathogen (claim 210), specifically BRSV (claim 211) in a bovine comprising administering a DNA plasmid vaccine, substantially as described in part (a) of claim 1 of the instant application. However, the claims of U.S.S.N. 09/760,574 do not encompass, nor do they render obvious, the administration of the DNA vaccine or immunogenic or immunological composition of claim 1(a) in combination with the conventional or recombinant vaccine or immunogenic or immunological composition of claim 1(b).

Further, the issue of whether there is indeed double patenting is contingent upon whether the claims of the pending applications are indeed allowed. If, upon agreement as to allowable subject matter in this application, it is believed that there is still a double patenting issue, the necessary Terminal Disclaimer(s) will be filed at that time.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, are requested.

III. THE REJECTIONS UNDER 35 U.S.C. §112, 2ND PARAGRAPH ARE OVERCOME

Claims 1, 4, 5 and 16-19 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

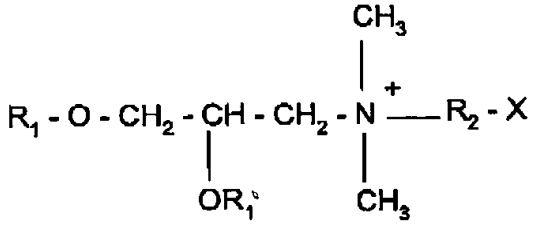
Claims 1 and 5 were amended to remove the non-limiting language, with the exception of one recitation of "and/or" in claim 5, which is believed to be acceptable. Dependent claims 21-37 have been added, as suggested by the Examiner on page 8 of the Office Action, to encompass the embodiments of the invention removed from claims 1 and 5.

In view of the amendments to the claims, reconsideration and withdrawal of the rejections under the second paragraph of 35 U.S.C. §112 are requested.

IV. THE REJECTION UNDER 35 U.S.C. §103 IS OVERCOME

Claims 1, 4, 5 and 16-19 were rejected under 35 U.S.C. §103, as allegedly being unpatentable over Taylor *et al.* in view of Harris *et al.* and further in view of Bonnem *et al.* and Baker *et al.* The rejection is traversed.

The present invention provides a method for obtaining an immunogenic response comprising administering to a bovine or porcine (a) a DNA vaccine or immunogenic or immunological composition against a bovine or porcine pathogen comprising at least one plasmid containing and expressing a nucleotide sequence encoding an immunogen of the bovine or porcine pathogen, and a cationic lipid containing a quaternary ammonium salt, of the formula



in which R_1 is a saturated or unsaturated linear aliphatic radical having 12 to 18 carbon atoms, R_2 is an aliphatic radical containing 2 or 3 carbon atoms, and X a hydroxyl or amine group and (b) an inactivated, attenuated live, subunit or recombinant vaccine or immunogenic or immunological composition against a bovine or porcine pathogen. The two vaccines or immunogenic or immunological compositions can be administered concurrently or sequentially. Sequential administration can include the use of a prime boost regimen, as described in the specification (for example, in the paragraph beginning on page 26, line 17).

The lipid can be DMRIE and the vaccine or composition can further comprise DOPE. The vaccine or composition can also further comprise GM-CSF or an expression vector containing and expressing a nucleotide sequence encoding GM-CSF.

The nucleotide sequence encoding the immunogen can have deleted therefrom a portion encoding a transmembrane domain, and the plasmid can further contain and express a nucleotide sequence encoding a heterologous tPA signal sequence, such as a human tPA signal sequence. Even further, the plasmid can further contain a stabilizing intron, such as intron II of a rabbit beta-globin gene.

In the elected species, the bovine pathogen is bovine respiratory syncitial virus (BRSV). The immunogen can be BRSV F or BRSV G. For instance, the immunogen can be BRSV F or G, modified by substitution of the BRSV F signal sequence with a human tPA signal sequence, and/or by deletion of the transmembrane domain and/or the C-terminal portion of the protein.

None of the cited documents teaches or suggests a method for obtaining an immunogenic response using DNA vaccine or immunogenic or immunological composition that comprises, *inter alia*, a plasmid that expresses DNA encoding an immunogen of a pathogen affecting

bovines or porcines in combination with a "conventional" (i.e. inactivated, attenuated live or subunit) or recombinant vaccine or immunogenic or immunological composition. Furthermore, none of the cited documents teaches or suggests the sequential use of such vaccines or compositions, particularly in a prime boost regimen.

For a Section 103 rejection to be proper, there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings to arrive at the claimed invention. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is additionally respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Furthermore, MPEP 2143.01 and 2143.02 mandate that for a Section 103 rejection to be proper, there must be some suggestion or motivation to modify reference teachings, and there must be a reasonable expectation of success.

To that end, a well-known problem in the art, especially as to multivalent compositions, involves "efficacy interference", namely a failure of one or more antigens, in a combination composition to maintain or achieve efficacy. This is believed due to interference with respect to that antigen's ability to stimulate an immunological, antigenic, antibody, or protective response in the host, e.g., bovine or porcine, when administered, because of the presence of the other antigens. For instance, rabies antigens in a combination with other antigens suffer interference from or interfere with the stimulation of an immunological, antigenic, antibody or protective response by those other antigens in such a composition, especially when that composition is administered to dogs.

Therefore, one skilled in the art, appreciating the problem of efficacy interference, would not have a reasonable expectation of success in combining the vaccine, immunogenic or immunological compositions of parts (a) and (b) of claim 1 to obtain an immunological response.

Success, in this instance, was demonstrated by the data presented in the current application. Examples 16 and 17, show that a mixture of DNA plasmid vaccines against BHV-1 and PRV, respectively, were efficacious. These Examples directly demonstrate that the method of claim 1, namely, producing an immunological response in vaccinated animals using at least two DNA vaccines or immunogenic or immunological compositions against a bovine or porcine pathogen, wherein at least one of the vaccines or compositions also contains a cationic lipid, is effective. This is contrary to what the skilled artisan might expect, given the known problem of efficacy interference in the art.

Turning to the cited references, Taylor *et al.* does not teach or suggest anything pertaining to a DNA plasmid vaccine, as recited in claim 1(a)(i) of the present application; but rather, relates to a vaccinia virus vaccine. There is nothing in the art, or in any of the cited documents, that allows one to extrapolate teachings and suggestions as to a vaccinia virus vaccine – a poxvirus vaccine – to a DNA plasmid vaccine. A recombinant vaccinia virus, as in Taylor, is an enveloped poxvirus, not a DNA plasmid, as called for by the instant claims. The skilled artisan does not equate a recombinant vaccinia virus vaccine with a DNA plasmid vaccine, nor does the skilled artisan extrapolate from teachings and suggestions as to recombinant vaccinia virus vaccines to DNA plasmid vaccines.

Even if the vaccinia virus vaccine could be equated with the DNA plasmid that is a component of the current invention, and Applicants deny that it could, there are no teachings or suggestions in Taylor that would lead one of skill to combine the DNA vaccine or immunogenic or immunological composition comprising, *inter alia*, a plasmid that expresses DNA encoding an immunogen of a pathogen affecting bovines or porcines with a "conventional" or recombinant vaccine or immunogenic or immunological composition.

Harris *et al.* only provides information only on cationic amphiphiles and does not remedy the deficiencies of Taylor.

Bonnem *et al.* relates to the administration of GM-CSF protein as a vaccine adjuvant. Bonnem does not teach or suggest the administration of a nucleic acid molecule encoding GM-CSF in conjunction with a DNA vaccine of any kind, let alone the combination specified by claim 1. Bonnem does nothing to cure the deficiencies of Taylor, with or without Harris.

Baker *et al.* deals only with DNA encoding bovine GM-CSF. Nowhere in Baker is there any teaching or suggestion that GM-CSF protein could or should be administered as a

component of a DNA vaccine or be co-expressed in a DNA vaccine, let alone a vaccine comprising a DNA plasmid, a cationic lipid, and a conventional or recombinant vaccine, as in the instant claims. Thus, Baker fails to remedy the deficiencies of Taylor, Harris and Bonnem.

Therefore, the combination of Taylor, Harris, Bonnem and Baker does not result in the claimed invention, as this combination does not teach or suggest the instant invention, nor does it offer any expectation that the present invention would be successful, particularly in view of the problem of efficacy interference, which is commonly recognized in the art.

Reconsideration and withdrawal of the 35 U.S.C. §103 rejection are respectfully requested.

CONCLUSION

In view of these amendments and remarks, the application is in condition for allowance. Early and favorable reconsideration of the application, reconsideration and withdrawal of the rejections, and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

Thomas J. Kowalski
Reg. No. 32,147
Telephone: (212) 588-0800
Facsimile: (212) 588-0500

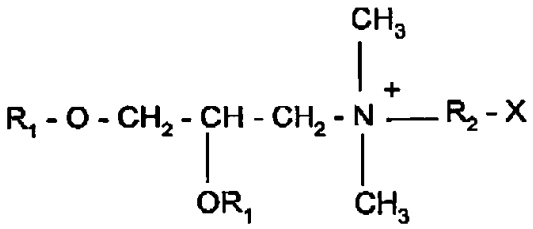
APPENDIX: CLEAN VERSION OF PENDING CLAIMS

1. (Amended) A method for obtaining an immunogenic response comprising administering to a bovine or porcine:

(a) a DNA vaccine or immunogenic or immunological composition against a pathogen of a bovine or porcine comprising:

(i) a plasmid containing and expressing a nucleotide sequence encoding an immunogen of a pathogen of the bovine or porcine; and

(ii) a cationic lipid containing a quaternary ammonium salt, of formula



in which R_1 is a saturated or unsaturated linear aliphatic radical having 12 to 18 carbon atoms, R_2 is another aliphatic radical containing 2 or 3 carbon atoms, and X a hydroxyl or amine group;

and

(b) an inactivated, attenuated live, subunit or recombinant vaccine or immunogenic or immunological composition against a bovine or porcine pathogen,

wherein (a) and (b) are administered together in a combination or sequentially.

2-3. (Withdrawn)

4. (Amended) The method according to claim 1 wherein the nucleotide sequence according to (a)(i) comprises a nucleotide sequence of BRSV.

5. (Amended) The method according to claim 4, wherein the nucleotide sequence of BRSV encodes F antigen and/or G antigen.

6-15. (Withdrawn)

16. (Original) The method of claim 1 wherein (a) and (b) are sequentially administered, whereby there is a first administration of (b), followed by a subsequent administration of (a).

17. (Amended) The method of claim 16, wherein (b) is an inactivated, attenuated live

or subunit vaccine or immunogenic or immunological composition.

18. (Amended) The method of claim 1, wherein the vaccine or immunogenic or immunological composition according to (a) further comprises DOPE.

19. (Amended) The method of claim 1, wherein the vaccine or immunogenic or immunological composition according to (a) additionally comprises a bovine or porcine GM-CSF protein or an expression vector containing and expressing a nucleotide sequence encoding the GM-CSF protein.

20. (Withdrawn)

21. (New) The method of claim 1, wherein the cationic lipid is DMRIE.

22. (New) The method of claim 1, wherein the nucleotide sequence encoding the immunogen has deleted therefrom a portion encoding a transmembrane domain.

23. (New) The method of claim 1, wherein the plasmid containing the nucleotide sequence encoding the immunogen further comprises a nucleotide sequence encoding a heterologous signal sequence.

24. (New) The method of claim 23, wherein the heterologous signal sequence is a tPA.

25. (New) The method of claim 1, wherein the plasmid containing the nucleotide sequence encoding the immunogen further comprises a stabilizing intron.

26. (New) The method of claim 25, wherein the stabilizing intron is intron II of rabbit beta-globin gene.

27. (New) The method of claim 1, wherein administration is sequential.

28. (New) The method of claim 27, wherein a prime boost regimen is used.

29. (New) The method of claim 5, wherein the nucleotide sequence of BRSV is optimized by substitution, by a heterologous signal sequence, of the signal sequence of the F antigen and/or G antigen of BRSV.

30. (New) The method of claim 29, wherein the heterologous signal sequence is from human tPA.

31. (New) The method of claim 5, wherein the nucleotide sequence of BRSV is optimized by deletion therefrom of a portion encoding a transmembrane domain of F antigen and/or G antigen.

32. (New) The method of claim 5, wherein the cationic lipid is DMRIE.

33. (New) The method of claim 32, wherein the vaccine or immunogenic or immunological composition of (a) further comprises DOPE.

34. (New) The method of claim 5, wherein the nucleotide sequence of BRSV encodes F antigen, and wherein the nucleotide sequence is optimized by:

(c) insertion of human tPA signal sequence in place of F antigen signal sequence; and

(d) deletion of the transmembrane domain and contiguous C-terminal portion.

35. (New) The method of claim 34, wherein the vaccine or immunogenic or immunological composition of (a) further comprises a second expression plasmid comprising a nucleotide sequence encoding BRSV G antigen, and wherein the nucleotide sequence encoding BRSV G antigen is optimized by:

(c) insertion of human tPA signal sequence in place of G antigen signal sequence; and

(d) deletion of the transmembrane domain and contiguous C-terminal portion.

36. (New) The method of claim 5, wherein administration is sequential.

37. (New) The method of claim 36, wherein a prime boost regimen is used.

38. (New) The method of claim 1, wherein the pathogen of a bovine or porcine in (a) and (b) are the same pathogen.